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Attachment B

Exhibit 2

Rogers (2004). "Airway mucus hypersecretion in asthma: an undervalued pathology?"
Current Opinion in Pharmacology, 4:241-250

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Airway mucus hypersecretion in asthma: an undervalued pathology?

Duncan F Rogers

Airway mucus hypersecretion is a feature of many patients with asthma. It is indicative of poor asthma control and contributes to morbidity and mortality. Excess mucus not only obstructs airways but also contributes to airway hyperresponsiveness. Furthermore, asthma might have a specific mucus hypersecretory phenotype. Goblet cell hyperplasia and submucosal gland hypertrophy are shared with other hypersecretory diseases, such as chronic obstructive pulmonary disease; however, some features are different, including mucus plugging, mucus 'tethering' to goblet cells, plasma exudation, and increased amounts of a low charge glycoform of mucin (MUC)5B and the presence of MUC2 in secretions. Experimentally, most of the inflammatory mediators and neural mechanisms implicated in the pathophysiology of asthma impact upon the mucus hypersecretory phenotype. There is currently huge research interest in identifying targets involved in inducing mucus abnormalities, which should lead to the rational design of anti-hypersecretory drugs for treatment of airway mucus hypersecretion in asthma.

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Abbreviations

COPD chronic obstructive pulmonary disease
IL interleukin
MARCKS myristoylated alanine-rich C kinase substrate

Introduction

Airway mucus hypersecretion is an undervalued pathology. It has long languished as the 'ugly sister' to bronchoconstriction and eosinophilic inflammation in research into the pathophysiology of asthma. However, epidemiological studies demonstrate that mucus is a far from innocent disorder [1]. Indeed, current guidelines on asthma management highlight mucus plugging (Figure 1) alongside bronchoconstriction and inflammation as a cause of airway obstruction and airflow limitation [2]. Consequently, it is important to understand the patho-

physiology of mucus hypersecretion in asthma. This should allow identification of therapeutic targets and subsequent rational development of pharmacotherapeutic drugs. This review focuses on the pathophysiology of mucus hypersecretion in asthma by, firstly, describing the mucus hypersecretory phenotype as it pertains to asthma; secondly, assessing the pathophysiological consequences and clinical impact of mucus hypersecretion in asthma; and thirdly, considering the epidemiology of mucus hypersecretion in asthma. The article finishes by outlining conventional and novel therapies for this condition.

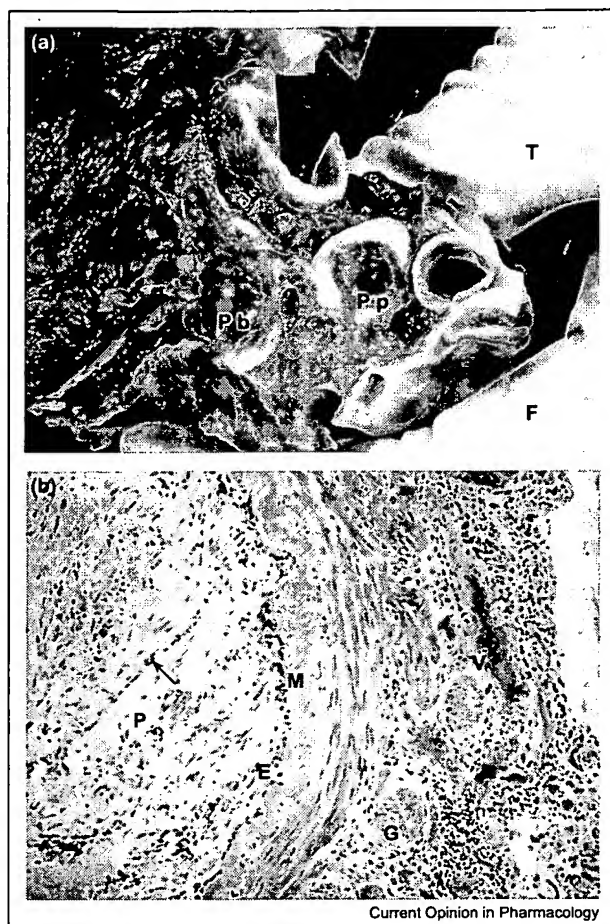
Airway mucus

In healthy individuals, a film of slimy liquid protects the airway surface from inhaled 'insult' [3*]. The liquid is referred to as 'mucus' and is a complex non-homogeneous dilute (1–2%) aqueous solution of electrolytes, endogenous and exogenous proteins, lipids and carbohydrates. Mucus forms an upper gel layer and a lower sol layer. Inhaled particles are trapped in the gel and, by transportation on the tips of beating cilia, are removed from the airways: a process termed mucociliary clearance. Mucus contains ~2% mucins [4*], which are high molecular weight glycoproteins that confer the viscoelasticity required for efficient mucus-cilia interaction. Airway mucins are secreted by goblet cells in the surface epithelium [5] and mucous cells in the submucosal glands [6]. Mature mucins are long thread-like molecules composed of monomers joined end to end by disulphide bridges. The mucin monomers comprise a highly glycosylated linear peptide sequence, termed apomucin, which is encoded by specific mucin genes (MUCs). Of the 18 human MUC genes reported to date, MUC5AC and MUC5B gene products are the major gel-forming mucins in airway secretions [4*], although MUC2 might be upregulated in asthma (see below) (Figure 2).

Mucus hypersecretory phenotype in asthma

Airway mucus hypersecretion in asthma has characteristic pathophysiological features. Many of these features, such as sputum production and goblet cell hyperplasia, are common to other hypersecretory respiratory diseases; for example, chronic obstructive pulmonary disease (COPD) and cystic fibrosis. Other features appear to be specifically associated with asthma (see below). Differences in mucus pathophysiology between asthma and COPD have been discussed previously [7], and are summarized in Figure 2. Presumably, differences between the pulmonary inflammatory 'profiles' of asthma and COPD (the former essentially a Th2 lymphocyte-driven eosinophilia, the latter a macrophage-driven neutrophilia) [8] underlie the

Figure 1



Airway mucus plugging in asthma. (a) Gross pathology of the lung from an asthmatic patient showing gelatinous plugs blocking (Pb) or partially occluding (Pp) large airways. Courtesy of Dr Catherine Corbishley whose gloved thumb (T) and finger (F) are holding the specimen. (b) Histology of an intrapulmonary airway of an asthmatic patient showing occlusion of the lumen by a mucus plug (P) with a marked infiltration of inflammatory cells (arrow). E, epithelium (damaged); G, submucosal gland; M, reticular basement membrane (thickened); V, blood vessel (with evidence of vasodilatation).

variations in hypersecretory phenotype of these two conditions. Although mucus abnormalities are considered a feature of asthma, it is not clear whether these abnormalities result from excessive production of mucus, an intrinsic biochemical abnormality in asthmatic mucus, interactions between mucus and other airway components, or a combination of any or all of these factors. These possibilities are addressed below.

Characteristics of mucus hypersecretion in asthma

Mucus plugging of the airways is a feature of fatal asthma in both adults and children [9*,10*] (Figure 1). Unlike those in COPD, airway plugs of asthmatic patients are difficult to dislodge from the airways [11]. The plugs

comprise plasma proteins, DNA, cells and proteoglycans, with mucins being the major gel-forming component [12]. Mucus plugging is not found in all patients dying of asthma; however, incomplete plugs often encrust the airways of asthmatic subjects who have died from causes other than their asthma [9*]. The latter observation indicates that plug formation is a chronic process that progresses to airway occlusion.

Markedly increased amounts of mucus are found throughout the airways of chronic asthmatic patients and in severe fatal asthma [9*,13,14*] (Figure 3). The increased luminal mucus is associated with sputum production, particularly during or just after acute attacks [15]. Increased sputum production is associated with increased mucus secretion, as determined by elevated mucin markers in sputum [16,17]. Several other molecules are also increased in asthmatic sputum, including DNA, lactoferrin, eosinophil cationic protein and plasma proteins (e.g. albumin and fibrinogen) [18]. Thus, increased mucin secretion, plasma exudation and inflammatory cell secretion are associated with mucus hypersecretion and sputum production in asthma.

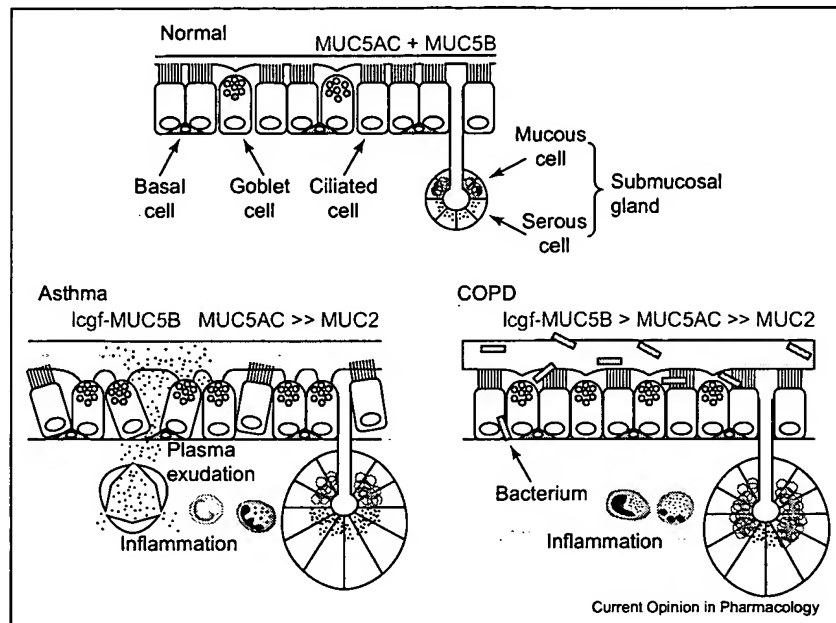
Increased mucin output reflects an increased amount of airway secretory apparatus. Submucosal gland hypertrophy is a pathophysiological feature of asthma, with the size of the glands increased two- to four-fold above controls (Figure 4) [13,14*,19]. However, gland hypertrophy is not common to all patients, even those with sputum production [20]. As a result, inflammation 'score' is a better morphological correlate of airway mucus hypersecretion than is gland size. Thus, although submucosal gland hypertrophy contributes to excess luminal mucus, glands of normal size can hypersecrete, presumably because of the influence of other factors, in particular airway inflammation.

Goblet cell hyperplasia is another pathophysiological feature of asthma, with an increased area and number of goblet cells found throughout the lower airways of patients with asthma [5,21*]. Again, goblet cell hyperplasia is not common to all patients. In a small cohort of Japanese asthmatics, goblet cells were increased markedly in acute severe patients but not in the airways of patients with chronic asthma (Figure 5) [13]. The degree of gland hypertrophy was similar between the two patient groups (Figure 4). The latter observations require confirmation but indicate that, in fatal asthma, airway submucosal gland hypertrophy is a non-specific feature, whereas disproportionate goblet cell hyperplasia is associated with, and possibly contributes to, deaths from asthma.

Mucus abnormalities asthma

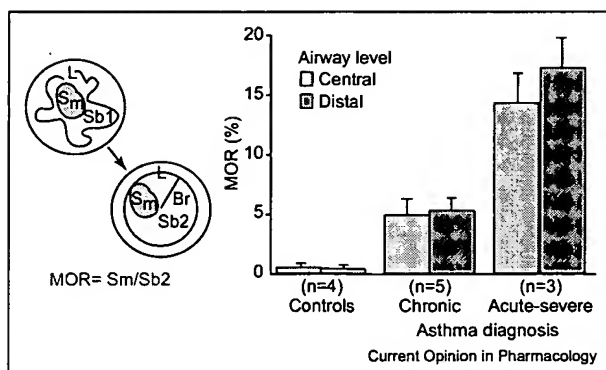
Is there an intrinsic biochemical abnormality of mucus in asthma? The viscosity of asthmatic sputum is greater than that of patients with COPD or bronchiectasis [16,22,23].

Figure 2



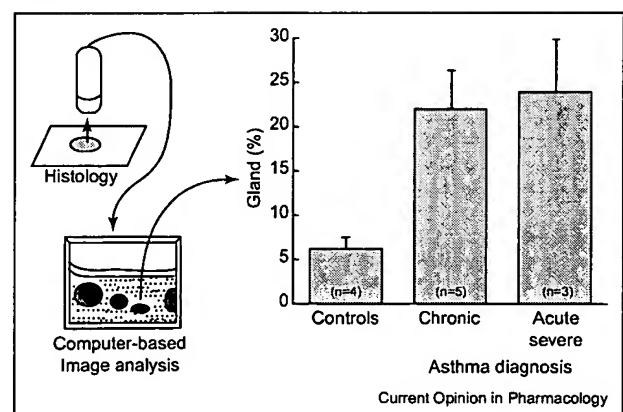
Mucus pathophysiology in asthma and COPD: similarities and differences. In asthmatics, there is increased luminal mucus, a similar or increased ratio of mucin (MUC) 5B (low charge glycoform [lgcf]) to MUC5AC, small amounts of MUC2, epithelial 'fragility', marked goblet cell hyperplasia, submucosal gland hypertrophy (with normal mucous to serous cell ratio), 'tethering' of mucus to goblet cells, and plasma exudation. Airway inflammation involves T lymphocytes and eosinophils. In COPD, there is increased luminal mucus, an increased ratio of lgcf MUC5B to MUC5AC, small amounts of MUC2, goblet cell hyperplasia, submucosal gland hypertrophy (with an increased proportion of mucous to serous cells), and respiratory infection (possibly owing to reduced bacterial enzymatic 'shield' from reduced serous cell number). Pulmonary inflammation involves macrophages and neutrophils. Many of these differences require data from greater numbers of patients.

Figure 3



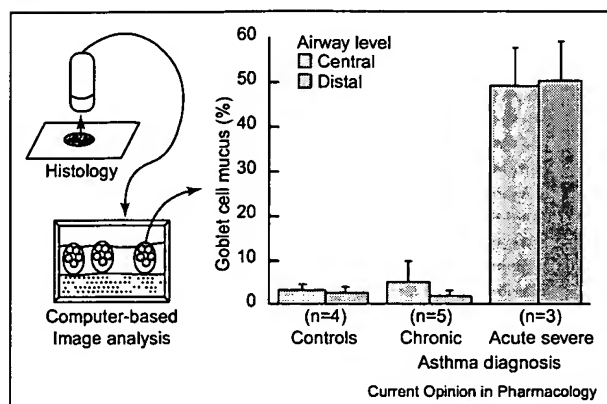
Airway luminal mucus in asthma. Area of luminal mucus was quantified morphometrically in histological sections of autopsied lungs of patients without lung disease (controls), patients with chronic asthma, or patients who had died of a sudden attack. Mucus occupying ratio (MOR) is significantly greater in both central and distal airways of patients who die with a diagnosis of asthma compared with controls. Br, bronchial radius; L, luminal perimeter; S_m , size of stained area of mucus; S_{b1} , size of bronchus before computer-based image analysis conversion to a circle, S_{b2} . Redrawn using data from [13].

Figure 4



Submucosal gland hypertrophy in asthma. Gland area was quantified morphometrically and expressed as the proportion of gland to bronchial wall in histological sections of autopsied lungs of patients without lung disease (controls), patients with chronic asthma, or patients who had died of a sudden attack. Redrawn using data in [13].

Figure 5



Goblet cell hyperplasia in asthma. The area of stained goblet cell mucin was quantified morphometrically and expressed as the proportion of mucin to total epithelial layer in histological sections of autopsied lungs of patients without lung disease (controls), patients with chronic asthma, or patients who had died of a sudden attack. Redrawn using data in [13].

Mucus plugs from a patient dying of asthma have notably different cross-linking, size, acidity and appearance (assessed by electron microscopy) compared with control mucus [12]. Characteristics of the mucins could explain the solidity of the mucus plugs; the authors concluded that the asthmatic mucus gel was stabilized by non-covalent interactions between extremely large mucins assembled from 'normal' sized subunits. This implies an abnormality in the mucin molecule assembly process. Although confirmatory studies are required, this investigation represents the first reliable demonstration of an intrinsic abnormality in mucus in asthma.

Is the abnormality in mucus caused by the presence, or absence, of a specific mucin species in asthmatic secretions? The MUC5AC gene product and a low charge glycoform of MUC5B are the major mucin species in airway secretions from patients with asthma [7,24*,25,26]. Both mucins are increased above the levels found in secretions from control subjects, in particular the low charge glycoform of MUC5B [24*,26–28]. Accumulating data indicate that in 'irritated' airways, including those in asthma, MUC2 and MUC5B become significantly expressed in goblet cells, in which MUC5B is normally found at low levels and MUC2 not at all [4*]. A correlate of this is that MUC2 gene expression is raised in the airways of asthmatic patients [29]; MUC2 mucin is detected in induced sputum from only one healthy subject out of 15, but was present in sputum from three out of six asthmatic patients [24*]. Studies in more patients are required to confirm if upregulation of MUC2 occurs in asthma. Whether or not incorporation of small quantities of MUC2, an insoluble mucin, in the asthmatic mucus gel has a pathophysiological correlate could then be examined.

Interactions between mucus and other airway components

Airway mucus in asthma is composed of numerous constituents other than mucins (see above). In experimental systems, several of these constituents interact with mucin in a way that is detrimental to airway homeostasis. Increased plasma exudation from the bronchial microvasculature into the airway lumen is a feature of asthma [30]; this plasma increases luminal liquid volume and stimulates mucus secretion, thereby further increasing liquid volume. *In vitro*, plasma albumin and DNA (also found in asthmatic sputum) synergistically increase mucus viscosity. There is little evidence that this happens *in vivo* in asthmatic patients, at least not at the concentrations of albumin and DNA found in asthmatic sputum. However, the combined effect might be sufficient to affect mucus viscosity. Thus, plasma exudation can directly and indirectly increase the amount of airway mucus, with albumin and DNA possibly increasing mucus viscosity.

Another possible interaction might occur between newly secreted mucin and inflammatory cell products. Mucin appears to be 'tethered' to goblet cells in fatal asthma, which is in contrast to patients with chronic bronchitis or control subjects [31]. The favoured explanation of the authors is that, in chronic bronchitis, proteases from neutrophils, the predominant inflammatory cell in the airways in COPD [8], cleave mucins attached to the cell surface of goblet cells. Eosinophils, rather than neutrophils, are the predominant inflammatory cell in asthmatic airways, and certainly predominated in the airways of the patients in the above study [31]. There is no evidence that eosinophil products are able to cleave mucins. Thus, 'tethering' of secreted mucin to goblet cells is specific to asthma, with the lack of neutrophils in the airways of patients dying of asthma contributing to mucus plugging. This hypothesis needs formal investigation.

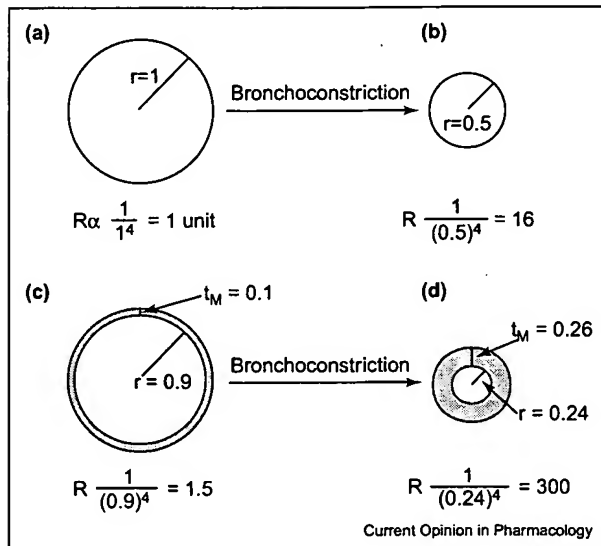
Pathophysiological consequences of mucus hypersecretion and hyperviscosity

The previous section established that there is overproduction of hyperviscous mucus in asthmatic airways. Depending upon how much is present, increased mucus in the airway lumen might not noticeably affect airflow (Figure 6). Larger quantities may still not affect airflow, but might induce cough that contributes markedly to patient morbidity [32]. In asthma, there are two main potential consequences of abnormal airway mucus: airway obstruction and increased airway responsiveness.

Airway obstruction

Airway obstruction with mucus and partially formed or complete mucus plugs is a feature of asthma (see above). Airway obstruction by mucus develops as a result of a combination of mucus abnormalities and ciliary dysfunction, leading to reduced mucociliary clearance, mucostasis and plugging. Excess mucus compromises small diameter

Figure 6



Theoretical amplifying effect of luminal mucus on airflow resistance in asthma. (a) According to Poiseuille's law, resistance to flow (R) is proportional to the reciprocal of the radius (r) raised to the fourth power. (b) Without luminal mucus, bronchoconstriction to reduce the airway radius by half increases airflow resistance 16-fold. (c) A small increase in mucus thickness (t_M), which reduces the radius of the airway by only one-tenth, has a negligible effect on airflow in the unobstructed airway (compare with panel a). (d) With bronchoconstriction, the same amount of luminal mucus markedly amplifies the airflow resistance of this airway.

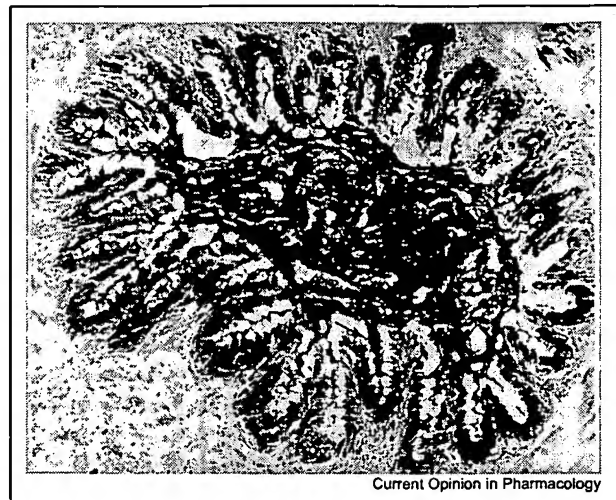
airway patency more easily than it does large diameter airways. Luminal liquid also produces an inward force owing to surface tension, further compromising airway patency [33]. Mucus clearance is impaired in all stages of asthma, including patients in remission [34]. Factors other than excess mucus can reduce clearance; these include epithelial damage and shedding (with consequent loss of cilia), goblet cell hyperplasia replacing ciliated cells [5], and the generation of mediators that slow mucociliary clearance directly (e.g. leukotriene D_4).

Obstruction of the airways leads to ventilation/perfusion mismatch [35]. Mucus obstruction in the asthmatic lung is patchy, which diverts ventilation from some alveolar regions to others to produce mismatch. There follows arterial hypoxaemia and stimulation of chemoreceptors, leading to hyperventilation and dyspnoea. Luminal mucus also contributes to increased airway resistance and the work of breathing.

Change in airway responsiveness

A reduction in airway luminal cross-sectional area will amplify any increase in airflow resistance due to bronchoconstriction (Figure 6). This exaggerated response is known as airway hyperresponsiveness, and is a clinical characteristic of asthma [36]. Airway wall thickening,

Figure 7



Effect of bronchoconstriction and luminal mucus on airway calibre in asthma. Marked bronchoconstriction in an intrapulmonary airway of a patient who died of an acute severe attack has thrown the epithelium (E) into tight, concertina-like folds. In the unobstructed airway (approaching circular in cross section), the comparatively small amount of intraluminal mucus might not have a significant effect on resistance to airflow (see Figure 6). However, the combination of intraluminal mucus and bronchoconstriction has occluded this airway. Arrow, mucus filling interstices between epithelial folds.

increased surface tension at the air-liquid interface, reduced external support of the airway wall, and increased luminal mucus all reduce airway cross-sectional area. Experimental introduction of small glass beads into the airways of anaesthetized and mechanically ventilated cats to mimic increased luminal mucus leads to marked airway hyperresponsiveness [37]. Even small increases in luminal liquid lead to marked airflow limitation with bronchoconstriction (Figure 7) [38]. However, excessive luminal mucus can have variable effects on airway responsiveness to inhaled spasmogens [39,40]. Responsiveness can either fall or increase, depending upon the pattern of distribution of mucus in the airways, which is usually not homogeneous [41,42]. Mucus accumulation in particular regions of the lungs results in uneven flow distribution. Inhaled bronchoconstrictors are then directed to less resistant airways, thereby amplifying their responsiveness.

Epidemiology of mucus hypersecretion in asthma

The detrimental effects of excess mucus on airway mucociliary clearance, luminal patency and airway reactivity outlined above should have concomitant detrimental effects on the asthmatic patient. Certainly, phlegm production (indicative of airway mucus hypersecretion) is an index of poor asthma control [2]. The greatest risk for increased mortality in asthma is decreased lung function, with a significant proportion of the excess risk

associated with mucus hypersecretion [1]. Some of the decrease in lung function will be caused by luminal mucus. Mucus hypersecretion is also a predictor of an excess decline in lung function, although not in all patients. Thus, in general terms, chronic airway mucus hypersecretion is associated with increased morbidity and mortality in patients with asthma. The following section addresses the issue of the derivation of this increased mucus output.

Generation of the airway mucus hypersecretory phenotype in asthma

Most of the numerous inflammatory mediators produced in asthmatic airways, together with neural mechanisms, can theoretically generate the mucus hypersecretory phenotype in asthma. In experimental studies, these mediators and neural mechanisms increase mucin secretion, induce plasma exudation, upregulate MUC gene expression, increase mucin synthesis and cause goblet cell hyperplasia (summarized in Table 1) [43–45]. Th2 lymphocyte-mediated generation of the mucus hypersecretory phenotype in animal models of asthma, and the pivotal involvement of interleukin (IL)-9 and IL-13 in

the induction of goblet cell hyperplasia, are well documented [46–49]. Other inflammatory cells involved include mast cells and neutrophils; both of these infiltrate submucosal glands in the airways of asthmatic patients [14^{*}]. Degranulation of mast cells is associated with increased luminal mucus. Mast cells secrete histamine and proteases, whereas neutrophils secrete elastase. These mediators all have effects on mucus in experimental systems [45]. Most of the above pathways operate through the epidermal growth factor receptor and its tyrosine kinase intracellular signalling cascade [50]. Another key element that appears to be involved in the asthmatic hypersecretory phenotype is the human calcium-activated chloride channel [51,52^{*}]. The Na⁺/K⁺/Cl⁻ cotransporter isoform 1 is also associated with mucus hypersecretion in asthma [53]. Thus, there are many possible targets for development of antihypersecretory drugs in asthma.

Pharmacotherapy of mucus pathophysiology in asthma

Airway mucus contributes to morbidity and mortality in many asthmatic patients; consequently, drugs affecting

Table 1

Potential mediators of airway mucus secretion, goblet cell hyperplasia, MUC synthesis/gene expression and plasma exudation in asthma.

Stimulation	Secretion	Hyperplasia	MUC	Plasma exudation
Cytokines				
IL-1 β	+	NP	NP	NP
IL-6	+	NP	Yes	NP
IL-9	NP	NP	Yes	NP
IL-13 (IL-4)	+	Yes	Yes	NP
TNF α	++	Yes ^a	Yes ^a	NP
Gases				
Irritant gases (e.g. cigarette smoke)	++	Yes	Yes	+
Nitric oxide	-ve/+	NP	NP	+
Reactive oxygen species	0/+	NP	NP	+
Inflammatory mediators				
Bradykinin	+	NP	NP	++
Cysteinyl leukotrienes	++	NP	NP	++
Endothelin	0/+	NP	NP	+
Histamine	+	NP	NP	++
PAF	+	Yes ^a	Yes ^a	+++
Prostaglandins	0/+	NP	NP	0/+
Proteinases	+++	Yes	NP	NP
Purine nucleotides	++	NP	NP	NP
Neural pathways				
Cholinergic nerves	++	NP	NP	0
Cholinergic agonists	++	Yes	NP	0
Nicotine	++	Yes	NP	++
Tachykinergic nerves	+	NP	NP	++
Substance P	++	NP	NP	+++
Neurokinin A	+	NP	NP	++
Miscellaneous				
EGF (+ TNF α)	NP	Yes	Yes	NP
Sensitisation followed by challenge	+	Yes	Yes	++

^aEffect only observed with PAF and TNF α in combination. +++, highly potent; ++, marked effect; +, lesser effect; 0, minimal effect; EGF, epidermal growth factor; NP, effect not published; PAF, platelet activating factor; TNF α , tumour necrosis factor- α .

Table 2

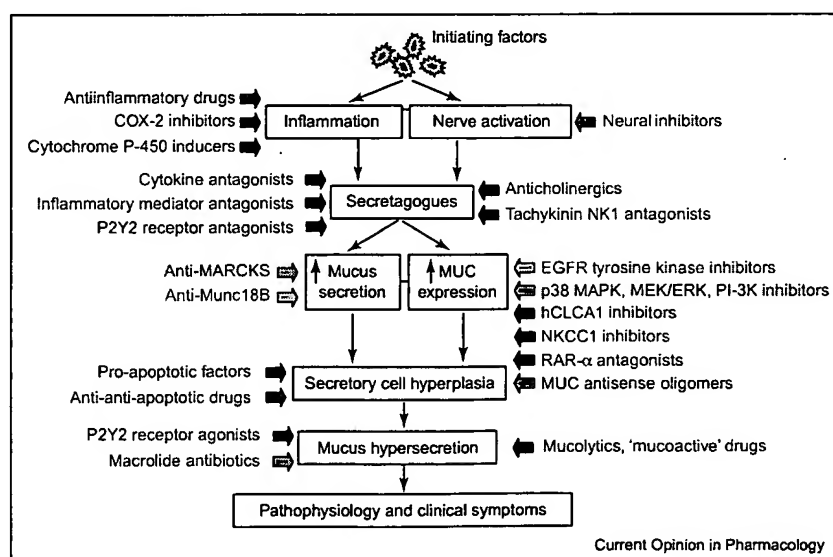
Theoretical objectives for effective pharmacotherapy of airway hypersecretory pathophysiology in asthma.

Overall objective	Specific objectives
Facilitate mucus clearance (short-term relief of symptoms)	Inhibit mucin secretion Inhibit plasma exudation Reduce mucus viscosity (increase elasticity) Increase ciliary function Induce cough
Reverse hypersecretory phenotype (long-term benefit)	Facilitate release of 'tethered' goblet cell mucin Treat airway inflammation Reduce goblet cell number Reduce submucosal gland size Inhibit increased production of low charge glycoform of MUC5B Inhibit production of MUC2 Reverse increased MUC5B:MUC5AC ratio

the hypersecretory component of asthma should be beneficial in these patients. Asthma has specific trigger factors, its own 'profile' of pulmonary inflammation and its own mucus hypersecretory phenotype (Figure 2); therefore, specific drugs might be required to fulfil the objectives for treatment of hypersecretion in asthma (Table 2). Pharmacotherapy of airway mucus hypersecretion in asthma has been discussed in detail recently [45] and is summarized herein (Figure 8; Table 3). Essentially, pharmacotherapy can be divided into two sections: firstly, anti-inflammatory treatment of airway inflammation, probably the most beneficial therapy overall; and sec-

ondly, therapies directed specifically at different levels of the pathophysiological 'cascade', from secretagogues to clinical symptoms (Figure 8). Many potential therapies are undergoing intensive investigation; for example, myristoylated alanine-rich C kinase substrate (MARCKS) is fundamental to goblet cell mucin exocytosis [54]. A synthetic peptide corresponding to the N-terminal domain of MARCKS inhibits airway mucin secretion in a mouse model of asthma [55*]. However, with the exception of glucocorticosteroids, it is unlikely that any single class of compound will provide comprehensive treatment of mucus hypersecretion in asthma.

Figure 8



Pharmacotherapy of airway mucus hypersecretion in asthma. The pathophysiological 'cascade' from initiating factors to clinical symptoms can be accessed at different levels by 'antihypersecretory' pharmacotherapeutic compounds. The precise site(s) of action of many compounds is unclear, and some compounds might act at more than one site. hCLCA, human calcium-activated chloride channel; COX, cyclooxygenase; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase kinase; MUC, mucin (gene); NKCC, Na⁺-K⁺-Cl⁻ cotransporter; PI3K, phosphatidylinositol 3-kinase; RAR, retinoic acid receptor.

Table 3

Potential therapeutic targets and inhibitors of airway mucus hypersecretion in asthma.

Target	Inhibitors
Airway inflammation	Glucocorticosteroids (e.g. ciclesonide), PDE4 inhibitors (e.g. cilomilast, roflumilast), suplatast tosilate, cytokine/chemokine blockers (monoclonal antibodies, soluble receptors, small molecule inhibitors and receptor antagonists), macrolide antibiotics (erythromycin, flurythromycin), iNOS inhibitors (e.g. GW273629, L-NIL), COX-2 inhibitors (e.g. rofecoxib, celecoxib), cytochrome P-450 inducers (e.g. benzaifibrate), HO inducers (see Update)
Mucus properties	
Thickened mucus	Mucolytic drugs (e.g. <i>N</i> -acetylcysteine, nacystelyn)
P2Y ₂ receptors	Selective agonists for mucus hydration (e.g. INS37217)
Goblet cell hyperplasia	
Bcl-2	Antisense oligonucleotides (e.g. G3139 [Genasense, oblimersen]), Bax mimetics
hCLCA1	Talinflumate
EGFR tyrosine kinase	AG1478, BIBX1522, ZD1839 (Iressa)
ERK	MEK inhibitors (e.g. PD98059, U0126)
MUC gene expression	18-mer MUC antisense oligonucleotide
NKCC1	Bumetanide
p38 MAPK	p38 MAPK inhibitors (e.g. SB 203580)
PI3K	PI3K inhibitors (e.g. LY-294002)
Inflammatory mediators	
Bradykinin (B ₂ receptors)	Icatibant
Endothelin-1 (ET _A receptors)	Bosentan
Cysteinyl leukotrienes (Cys-LT ₁ receptors)	Montelukast, zafirlukast
Mast cell tryptase	APC-366, BABIM
Neutrophil elastase	Elastase inhibitors (e.g. batimastat, suramin and macrolide antibiotics such as erythromycin and flurythromycin)
PAF	Apafant, modipafant
P2Y ₂ purinoceptors	P2Y ₂ antagonists (none yet available)
Mucin exocytosis	
MARCKS	MARCKS inhibitors (e.g. MANS peptide)
Munc-18B	Munc-18B inhibitors (antisense oligomer)
Neural pathways	
Nerve activation	VR-1 receptor antagonists (e.g. anandamide, capsazepine)
Neurotransmitter release	BK _{Ca} channel activators (e.g. NS 1619), CB ₂ receptor agonists (e.g. AM1241, SR144528)
Muscarinic (M ₃) receptors	Anticholinergics (e.g. ipratropium bromide, tiotropium)
Tachykinin NK ₁ receptors	Tachykinin NK ₁ receptor antagonists (e.g. CP99,994, RP67580, noltipantium; dual NK ₁ /NK ₂ and triple NK ₁ /NK ₂ /NK ₃ antagonists)

BABIM, bis(5-amidino-2-benzimidazolyl)methane; CB, cannabinoid; CLCA, calcium-activated calcium channel; COX, cyclooxygenase; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; HO, heme oxygenase; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; MUC, mucin; NK, neurokinin; NKCC, Na⁺/K⁺/Cl⁻ cotransporter; PAF, platelet activating factor; PDE, phosphodiesterase; PI3K, phosphatidylinositol 3-kinase; VR, vanilloid receptor.

Conclusions

Airway mucus hypersecretion and the pathophysiological changes that accompany it are features of many patients with asthma. The impact of airway hypersecretion on morbidity and mortality is now more fully understood, even though it can often be limited to certain groups of patients. Nevertheless, it is important to develop drugs that inhibit mucus hypersecretion in susceptible patients. Before addressing these issues, more information is required on mucus physiology and pathophysiology, particularly concerning the biochemical and biophysical nature of airway mucins in healthy subjects. Whether or not there is an intrinsic abnormality of mucus in asthma, and whether any abnormality is specific for asthma, requires confirmation. The factors that regulate MUC gene expression in health and dis-

ease, and the relationship between this regulation and development of an asthma-specific hypersecretory phenotype, need to be determined. The above information could then be used to delineate therapeutic targets which, in turn, should lead to rational design of anti-hypersecretory drugs for treatment of airway mucus hypersecretion in asthma.

Update

Induction of heme oxygenase, the enzyme that degrades heme, by repeated administrations of hemin demonstrates anti-inflammatory activity in a mouse model of allergic asthma, including inhibition of airway mucus hypersecretion (inhibition of upregulated MUC5AC gene expression and of increased periodic acid-Schiff staining of mucus) [56]. The inhibitory effects of hemin were

reversed by the heme oxygenase inhibitor tin protoporphyrin-IX.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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